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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,043	12/12/2006	Antje Gupta	4838-002	3865

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EXAMINER	
MEAH, MOHAMMAD Y	

ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
09/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,043	GUPTA ET AL.	
	Examiner	Art Unit	
	MD. YOUNUS MEAH	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 44-55 are pending.

Claim Rejections

Applicants' arguments filed on 6/11/08 have been fully considered and are not deemed to be persuasive to overcome some of the rejections previously applied. Rejections not reiterated from previous office actions are hereby withdrawn.

35 U.S.C 112 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 45-49, 52-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 52 is indefinite in the recitation of "stringent conditions" as the specification does not define what conditions constitute "stringent". While page 5 of the specification describes some conditions, which are intended to be stringent, there is nothing to suggest that other conditions would not also be included within the scope of this term and in the art what is considered stringent varies widely depending on the individual

situation as well as the person making the determination. As such it is unclear how homologous to the sequence of a gene encoding SEQ ID NO: 9, a sequence must be to be included within the scope of these claims.

Applicants' argument about stringent condition is considered but not found persuasive. The term is vague and has no metes and bound. In the art what is considered stringent varies widely depending on the individual situation, such as salt concentration, type of salt, temperature for washing, etc is varied in different stringent conditions depending on individual situation, as well as the person making the determination. Therefore a stringent condition used in one situation is not the same in another situation. It should be defined with salt concentration, temperature of washing, etc..

Claims 45, 47, 49 and 54 are rejected under 35 U.S.C. 112, second paragraph, as being unclear because a broad range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74

(Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 45 recites the broad recitation 80% t0 99.5% , and the claim also recites 99% to 99.5% which is the narrower statement of the range/limitation. Similarly claim 47 recites the broad recitation the genuses of Pichia, Candida and also the claim recites Pichia capsulate which is the narrower statement of the range/limitation. Similarly claim 49 recites the broad recitation 2 to 20 amino acids and the claim also recites 3 to 10 amino acids which is the narrower statement of the range/limitation. Similarly claim 54 recites the broad recitation 6 to 25 amino acids and the claim also recites 10 to 18 amino acids which is the narrower statement of the range/limitation.

Claim 46 is confusing in recitation " encoded by a DNA sequence according to SEQ ID NO: 8 and has the amino acid sequence according to SEQ ID NO: 9" because a DNA sequence according to SEQ ID NO: 8 may comprise fragment of SEQ ID NO: 8 yet fragments of SEQ ID NO:8 do not necessarily encode SEQ ID NO:9 as required by the remainder of the claim.. It is suggested that the claim be rewritten "The isolated oxidoreductase according to claim 44, which has the amino acid sequence according to SEQ ID NO: 9"

Claim 48 is confusing in recitation of "additional amount of 1 to 40 amino acids less than the oxidoreductase having the amino acid sequence of SEQ ID NO: 9" as "additional amount" and "less than" are contradictory of each other. It is unclear whether it means 1-40 amino acid residues have modification from SEQ ID NO: 9, 1-40

amino acids have been added to SEQ ID NO:9, 1-40 amino acids have been deleted from SEQ ID NO:9 or some thing else.

Claim 53 is confusing in recitation of " protein fragment, wherein it represents fragments of the amino acid sequence SEQ ID NO: 9, having a number of 5 to 30 amino acids per fragment" It is unclear whether the claim is limited to fragments comprising 5-30 amino acid of SEQ ID NO; 9, whether the fragments can have any modifications compared to SEQ ID NO:9 or something else.

Claim 55 is confusing in recitation of "A fusion protein, wherein it contains the oxidoreductase having the amino acid sequence SEQ ID NO: 9 or fragments of the amino acid sequence SEQ ID NO: 9, having a number of 5 to 30 amino acids which are connected via a peptide bond to a further polypeptide at the N-terminal or carboxy-terminal end. It is unclear what the fusion protein comprise of, is it comprise of fusion of SEQ ID NO: 9 or a fusion of a fragments comprising 5-30 amino acid residues of SEQ ID NO: 9 or is it a fusion of SEQ ID NO:9 to any 5-30 amino acid residues or something else.

35 U.S.C 112 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44-45, 47-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for oxidoreductase comprising SEQ ID NO: 9 that

react ethyl-4-chloro-3-oxobutanoic acid to (R)-ethyl-4-chloro-3- hydroxybutanoic acid or oxidoreductase having one or more alteration (addition or subtraction) of amino acid residues of SEQ ID NO: 9 and so that said oxidoreductase comprise an amino acid sequence having 95% sequence identity with SEQ ID NO:9 and convert ethyl-4-chloro-3-oxobutanoic acid to (R)-ethyl-4-chloro-3- hydroxybutanoic acid , does not reasonably provide enablement for any oxidoreductase having 70% to 80% sequence identity with SEQ ID NO:9 or any fragment comprising 5 amino acids thereof or any oxidoreductase coded by any DNA which hybridizes under any stringent conditions with DNA comprising SEQ ID NO:8 or complementary strand thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claim(s).

Claims 44-45, 47-55 are so broad as to encompass any oxidoreductase having 70% to 80% sequence identity with SEQ ID NO:9 or any oxidoreductase encoded by any DNA which hybridizes under any stringent conditions with DNA comprising SEQ ID

NO:8 or any fragment comprising 5 amino acids thereof. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number oxidoreductase broadly encompassed by the claims. In view of the great breath of claims 44-45, 47-55, amount of experimentation required to isolate polypeptide molecules having specific oxidoreductase activity from these enormous number of polypeptide molecules and , the lack of guidance, working examples, unpredictability of the art in predicting the function (oxidoreductase activity) from protein's structure the claimed invention would require undue experimentation. The genus of oxidoreductase variants recited in these claims, having 70-80% identity to SEQ ID NO: 9. comprise a large variable of genus that most of which would not convert ethyl-4-chloro-3-oxobutanoic acid to (R)-ethyl-4-chloro-3- hydroxybutanoic acid. While specific variant which do not convert ethyl-4-chloro-3-oxobutanoic acid to (R)-ethyl-4-chloro-3- hydroxybutanoic acid might react with other carbonyl compounds the specification provides no guidance for selecting such variants for the many other oxidoreductase functions encompassed by the claims. The specification discloses one working example, which is the oxidoreductase comprising the amino acid sequence of SEQ ID NO: 9 which convert ethyl-4-chloro-3-oxobutanoic acid to (R)-ethyl-4-chloro-3-hydroxybutanoic acid. However, the specification fails to disclose any specific guidance for altering the polypeptide of SEQ ID NO: 9 with the expectation that the variant polypeptide will have other oxidoreductase activities because guidance and working examples teaching unalterable structural and catalytic amino acid residues and amino acid residues tolerable to change is not provided by the specification. Therefore, in view

of the overly broad scope of the claims, the specification's lack of specific guidance and additional working examples, it would require undue experimentation for a skilled artisan to make and use the entire scope of the claimed invention.

Since the amino acid sequence of a protein encoded by a polynucleotide determine its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the sequence and respective codons in its polynucleotide, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the encoded proteins' structure relates to its function. However, in this case the disclosure is limited to one oxidoreductase (SEQ ID NO: 9).

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass any oxidoreductase having 70% t0 80% sequence identity with SEQ ID NO:9 or any fragment comprising 5 amino acids thereof or any oxidoreductase

encoded by any DNA which hybridizes under any stringent with DNA comprising SEQ ID NO:8 because the specification does **not** establish: (A) regions of the polynucleotide/protein structure which may be modified without oxidoreductase activity; (B) the general tolerance of oxidoreductase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any oxidoreductase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any polypeptide molecules encoding any oxidoreductase having any structure, or any oxidoreductase having any alteration of amino acid residues of SEQ ID NO: 9 or any oxidoreductase having 70% t0 80% sequence identity with SEQ ID NO:9 or any fragment comprising 5 amino acids thereof or any oxidoreductase coded by any DNA hybridizes under any stringent conditions with DNA comprising SEQ ID NO:8 or complementary strand thereof. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of an oxidoreductase gene, having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants argue in their amendment at page 5 that specification contained sufficient disclosure that one skilled in the art can make and the claimed invention. While as discussed by applicants the specification provides some guidance with regard to which amino acids of the enzyme can be modified, the guidance provided is much too general in nature to enable the full scope of the rejected claims. It is noted that 70-80% identity to 400 amino acid residue fragment of SEQ ID NO: 9 as recited in the claims encompass many enzymes having 30-20% non-identical sequences, i.e., 120-80 amino acid residues altered Claims 47-49 also recite a genus of oxidoreductase variants wherein said variants comprise 1 to 25 amino acid mutations of a polypeptide having 70% homology to SEQ ID NO: 9. The oxidoreductase comprising SEQ ID NO: 9 comprises a specific activity of converting ethyl-4-chloro-3-oxobutanoic acid to (R)-ethyl-4-chloro-3- hydroxybutanoic acid The genus of oxidoreductase variants recited in these claims, wherein said variants comprise 1 to 25 amino acid mutations of a polypeptide having 70% homology to SEQ ID NO: 9 or oxidoreductase having 70-80% identity to SEQ ID NO: 9. comprise a large variable of genus that it would not convert ethyl-4-chloro-3-oxobutanoic acid to (R)-ethyl-4-chloro-3- hydroxybutanoic acid.

While methods to produce a polynucleotide and/ or polypeptide or its variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants as claimed by applicants (i.e., polypeptide having 70% identical to 400 amino acid residue fragment of SEQ ID NO: 9 requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. With

only the limited guidance provided by the specification one of ordinary skill would be reduced to the necessity of producing and testing virtually all of the possibilities. This would clearly constitute **undue** experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification. As previously stated the specification does not establish: : (A) regions of the polynucleotide/protein structure which may be modified without oxidoreductase activity; (B) the general tolerance of oxidoreductase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any oxidoreductase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

CLAIM Rejection - 35 U.S.C 102

35 U.S.C 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that

an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 53-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Kojima et al. (US PAT 5763236). Kojima et al. teach a NADH dependent oxidoreductase (carbonyl reductase) comprising SEQ ID NO: 2 which is 48% identical to applicants SEQ ID NO: 9 and has 11 consecutive amino acid residues , residues 129-139 of SEQ ID NO: 2 are identical to residues 132 to 142 of applicants SEQ ID NO: 9 and therefore reads on applicants claims 53-55.

Applicants' amendments necessitate the above rejection and therefore the action made final.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-272-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Fax Cover Sheet

Date: 12 Sep 2008

To:	**From:** MD. YOUNUS MEAH
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☐ **Urgent** ☐ **For Review** ☐ **For Comment** ☐ **For Reply** ☐ **Per Your Request**

Comments:

Number of pages __ including this page